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Reply to Office Action mailed April 2, 2008

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4%. Accordingly, almost all of the eye drop concentration range of Thompson et al. falls outside of applicants' claimed range. Stated differently, Thompson et al. have no teaching or suggestion for an eye drop concentration as low as 0.01 %, as recited in applicants' claims and as set forth in applicants' Examples. Such low eye drop concentration, as claimed by the applicants, provides an excellent antipruritic effect. See Table 1 on page 11 of applicants' specification, which is reproduced as follows:

Table 1

test compounds	number of times of eye scratching	eye scratching behavior inhibition ratio (%)
Compound A (0.1%)	29.0	57.4
Compound A (0.01%)	44.6	34.4
Control	68.0	-

As is apparent from Table 1, the number of times eye scratching in the guinea pigs, to which the Compound A, {4-cyano-4-[3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl]piperidine-1-yl}acetic acid monohydrate, was administered, decreased significantly compared to the control. Compound A in the

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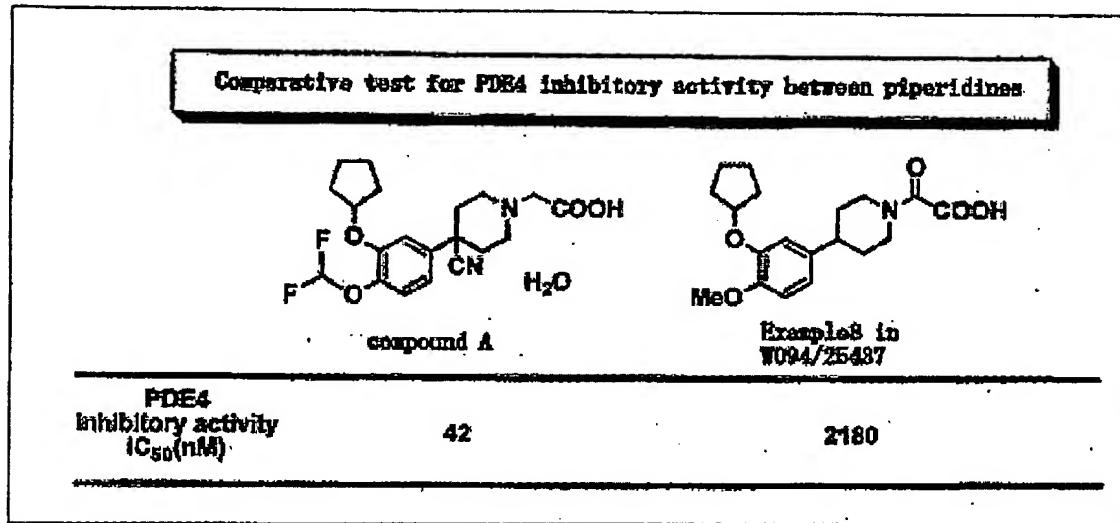
concentration recited in applicants' claims results in an excellent antipruritic effect.

As discussed above, the concentration of Compound A recited in applicants' claims is very desirable for inhibiting eye itching. With respect of the solubility of Compound A, it is submitted that the concentration of the compound recited in applicants' claims is considered to be beyond the expectation of a person having ordinary skill in the art.

Therefore, it is respectfully submitted that a person having ordinary skill in the art would encounter a difficulty in arriving at the appropriate concentration of the active ingredient in an eye drop, as recited in applicants' claims, in view of the pharmacological effects and other factors to be taken into consideration.

Compounds having a piperidine structure in common do not always result in the same pharmacological activity. See the following comparative test for PDE4 inhibitory activity between piperidines.

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The compound of WO 94/25437 is extremely similar to applicants' Compound A, both having not only a piperidine structure, but also structures of other functional groups (such as cyclopropyl and carboxyl groups) in common. The compound of WO 94/25437 has a significantly lower PDE4 inhibitory activity than applicants' Compound A. Therefore, compounds having a piperidine structure, such as in Thompson et al., do not always possess a PDE4 inhibitory activity.

It is stated in the Office Action that eye drops are typically made up at a concentration of active agent between

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about 0.1 to 4% in the ophthalmic medium in terms of the known solubility and stability of piperidines. However, applicants' present claims are directed to eye drops at a much lower concentration than 4%.

The aforesaid Table 1 of the present specification shows that an eye drop at a concentration of 0.1% has a greater effect than at a concentration of 0.01% with respect to an inhibitory effect on eye itching. The position was taken in the Office Action that an eye drop at a concentration higher than 0.1%, which overlaps with Thompson et al., would show a greater inhibitory effect. It was concluded in the Office Action that it cannot be said that the lower the concentration of the eye drop, the greater is the inhibitory effect. Applicants disagree with this conclusion for the following reason.

An eye drop at a concentration of 0.01 to 0.1% recited in applicants' present claims is able to meet the requirements of a pharmaceutical product in terms of solubility and stability and is able to exhibit a desirable inhibitory effect on eye itching. Consequently, it is respectfully submitted that the concentration

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of 0.01 to 0.1% of the particular compound recited in applicants' claims is not obvious from any references.

The position was taken in the Office Action that to determine the appropriate concentration of the Compound A as eye drops represents "obvious to try." Applicants disagree with this position. It is respectfully submitted that it is beyond the skill of a worker in this art to take into consideration the solubility and safety of the Compound A, as recited in applicants' claims, which was not known before the filing date of the present application (the monohydrate is not described in Nakai et al.) and to determine the optimum concentration of eye drops, in order to obtain an "inhibitory effect on eye itching" of Compound A. Such is not disclosed or suggested in any of the references.

It is therefore respectfully submitted that applicants' present claims are not rendered obvious over the references, in view of the many distinctions discussed hereinabove. Withdrawal of the 35 USC 103 rejection is respectfully requested.

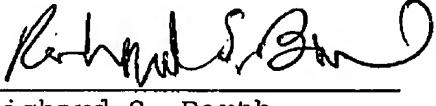
Reconsideration is requested. Allowance is solicited.

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If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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